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This address is also reflected in the substitute Declaration and Power of Attorney, mailed

Claims 1, 4, 6, 8-13, 15, 22-35 and 154-216 are presently pending.

THE REJECTION OF CLAIMS 22-29, 31, 32, 34 and 35 UNDER 35 U.S.C. § 103(a)

Claims 22-29, 31, 32, 34 and 35 are rejected under 35 U.S.C. § 103 as being unpatentable over June *et al.* (WO 94/29436 or U.S. Patent No. 4,804,628) in view of O'Garra *et al.* because June *et al.* allegedly teaches the method of claim 22 to where unfractionated T cells or CD4+ cells are expanded by treatment with anti-CD3 antibody followed by anti-CD28 or anti-CTLA4 or IL-2 treatment to expand the cells, which is alleged to produce Th1 cells; and O'Garra *et al.* teaches that stimulation of CD4+ cells in the presence of IL-2 or anti-CD3 produces Th1 cells and that anti-IL-4 antibody treatment produces Th1 cells. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to have to have produced the claims methods because June *et al.* teaches a method that produces Th1 cells and O'Garra *et al.* conditions that favor development of Th1 cells, and the ordinarily skilled artisan would have been motivated to have produced Th1 "for a variety of art-recognized purposes." This rejection is respectfully traversed.

The Examiner has failed to set forth a case of *prima facie* obviousness

(1) Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must

actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (BPAI 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)).

Teachings of the cited references

June *et al.*

The teachings of the June *et al.* references. Page 9 first complete paragraph of June *et al.*, does not teach differentiation of T cells into regulatory immune cells prior to expansion. In this paragraph, June *et al.* describes antigen specific activation of a population of cells. Preparing antigen-specific cells does not involve differentiation of cells to produce Th1 or Th2 (*i.e.*, regulatory immune cells) cells as claimed in the instant claims. Antigen-specific activation of a population of cells is not the same as production of Th1 or Th2 cells.

With respect to Table 2, as discussed above, June *et al.* specifically teaches the use of antibodies to CD3 or CD2 and antibodies to CD28 for expansion, not for differentiation. As an alternative, June *et al.* teaches use of IL-2 with anti-CD28 for induction of proliferation. Table 2 presents a comparison of the results of stimulation of proliferation using antibodies and either IL-2 or anti-CD28 as the co-stimulus **to induce activation/proliferation, not to induce differentiation.** There is no separate step of inducing differentiation into Th1 or Th2 cells, and then addition of activation/proliferation signals. June *et al.* teaches use activation/proliferation signals, such as anti-CD3 or IL-2 and

anti-CD28 for expansion, not for differentiation in to Th1 or Th2 cells prior to expansion.

Hence, there is not differentiation step as urged by the Examiner. IL-2 and anti-CD28 are added co-stimulants; IL-2 is not added for achieving differentiation, but to promote activation/proliferation. This is **not** the same as adding Il-2 for differentiation followed by two or more signals that promote activation/proliferation. The difference can be seen from the cytokine profiles of the resulting cells in Table 2.

The cytokine profiles of the resulting expanded cells are shown in Table 2 over several cycles of stimulation. The data in the Table clearly demonstrate that the combination of adding Il-2 or anti-CD3 **WITH** anti-CD28, followed by several additional cycles of anti-CD28 is different from method as claimed in the instant application. It does not result in regulatory cells as defined in the instant application, and certainly not in a homogeneous population of Th1 or Th2 cells. The step of adding IL-2 with anti-CD28 is **not a step that causes differentiation into regulatory cells**. The resulting cells even at that stage produce Il-4 as well as IFN-γ and IL-2, and the amount of Il-4 increases with each cycle of expansion. Hence, the resulting **expanded** cells are not Th1 or Th2.

Furthermore, the additional cycles in which only anti-CD28 are added do not meet the limitations of the instant claims, which require contacting with two or more activating proteins specific for cell surface proteins. If the first activation cycle is somehow construed to be a differentiation cycle, the subsequent cycles do not meet the limitations of the instant claims which require two or more activating proteins (to ensure a proliferative response).

It can be seen that by the third cycle of stimulation in the June *et al.* experiment, the expanded cells are producing IL-2, IFN-γ **AND** IL-4. Hence the resulting population of cells does not have characteristics of a homogeneous population of Th1 or Th2 cells, but rather has a mixed phenotype, which as discussed above is characteristic of undifferentiated precursor T_0 cells. These

cells, which produce IL-4 are clearly not Th1 cells. Since they produce IFN-γ, they cannot be Th2 cells. Hence there is no evidence that the June *et al.* produces Th1 cells, and certainly does not produce a homogeneous population of Th1 cells. Therefore, not only does June *et al.* not explicitly contemplate a method of differentiating cells followed by proliferation, June *et al.* does not inadvertently perform the instantly claimed methods; June *et al.* does not suggest preparation of homogeneous compositions of Th1 or Th2 cells.

June *et al.* does not teach methods for producing homogenous populations of expanded cells. June *et al.* is directed to methods for expanding lymphocytes in the absence of IL-2. Nowhere in June *et al.* is there a suggestion to first differentiate the cells, and then expand the differentiated cells.

O'Garra *et al.*

O'Garra *et al.* is background reference that describes the patterns of cytokines secreted by the different populations of T-cells and the manner in which Th1 and Th2 develop *in vivo*. It is not particularly relevant to the instant claims, does not cure the deficiencies of the teachings of June *et al.* O'Garra does not teach or suggest preparation of homogeneous populations of expanded Th1 or Th2 cells nor provide a motivation to prepare such cells.

There would have been no motivation to have combined the teachings of June *et al.* with O'Garra *et al.* and the combination does not result in the instantly claimed methods

Motivation

None of the cited references singly or in any combination thereof teaches or suggests anything regarding preparation of substantially **homogeneous populations of Th1 or Th2 cells**. None of the cited references suggests any method that involves restoration of the immune system balance by administration of compositions containing substantially only one type of

regulatory immune cell (Th1 or Th2). It is the instant application that provides such suggestion and motivation.

June *et al.* is directed to methods for expansion of cells; and does not suggest expansion of one type of cell for any purpose. As discussed above and in the response mailed July 5, 2000, June *et al.* the cells produced by the method of June *et al.* are clearly not homogeneous or predominantly Th1 or Th2 cells. The cytokine profile of the resulting cells (Table 2) is clearly that of a mixed population. This is because June *et al.* does not provide any suggestion for differentiation of cells into one type of cell **prior to expansion**.

The secondary references O'Garra *et al.* describe properties of Th1 and Th2 cells *in vivo* and explains *in vivo* establishment of lymphokine-producing phenotypes and development thereof. There is nothing in the teachings of this reference or June *et al.* that would have motivated combination of their teachings nor that would have motivated the ordinarily skilled artisan to produce homogeneous compositions of Th1 or Th2 cells.

Contrary to the assertion of the Examiner none of the art of record provides any uses for substantially compositions of expanded Th1 or Th2 cells.

Combination of teachings

Notwithstanding the lack of motivation, even if combined, the teachings of the cited references do not suggest expansion of Th1 or Th2 cells *in vitro* to produce compositions containing clinically relevant numbers of cells (more than 10^{10} cells, and particularly with respect to dependent claims, at a density of more than 10^{8} cells/ml) of predominantly Th1 or Th2 cells. June *et al.* is deficient in failing to teach or suggest a method in which cells are differentiated to one phenotype or the other and then expanded; O'Garra *et al.* does not cure this deficiency.

As discussed above, June *et al.* or June *et al.* in view of O'Garra *et al.* does not teach or suggest a method for obtaining clinically relevant numbers of T lymphoid cells (at least 10^{10} cells) nor expansion of such cells under

conditions that produce high cell density nor a homogeneous compositions. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

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In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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